Remarks

Claims 12-14, 44, and 45 were pending in the subject application. By this Amendment, claims 12-14 have been amended. The undersigned avers that no new matter is introduced by this Amendment. Support for the amendments can be found throughout the subject specification and in the claims as originally filed. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 12-14, 44, and 45 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

By this Amendment, claims 12-14 have been amended. Claim 12 has been amended to correct an obvious typographical error. Support for the amendments to claims 13 and 14 can be found, for example, at page 16, lines 7-22, of the specification as filed.

Claims 12-14, 44, and 45 are rejected under 35 USC §103(a) as obvious over McSwiggen *et al.* (U.S. Patent 5,693,532), in view of Tuschl *et al.* (U.S. Patent Publication 2004/0259247) and Chen *et al.* (U.S. Patent Publication 2004/0242518). Applicants respectfully traverse.

The McSwiggen *et al.* patent is cited in the Office Action for teaching methods of inhibiting the replication of RSV using ribozymes targeted to RSV NS1 and NS2 targets. The Tuschl *et al.* publication is cited for teaching that siRNAs provide greater gene silencing activities than ribozymes. The McSwiggen *et al.* patent contains no empirical data, *in vitro* or *in vivo*, demonstrating that the ribozymes can be effectively delivered to airway cells *in vivo* such that expression of the RSV gene or transcript in the airway cells and RSV titer in the subject are reduced. Example 2 of Tuschl *et al.* demonstrates gene silencing in mammalian cells *in vitro*; however, there is no empirical evidence in the cited references that the siRNAs can be effectively delivered to airway cells *in vivo* such that expression of the RSV gene or transcript in the airway cells and RSV titer in the subject are reduced. The cited references and the Office Action do not establish a correlation between the disclosed procedures and reduction in RSV viral titer in the human airway. In contrast, as described in application number 60/481,738, Applicants demonstrated that delivery of a vector carrying an NS1-targeting siRNA to human A549 alveolar type-II epithelial cells resulted in reduced NS1 expression and reduced RSV production (Figures 1B, 2A, 2B, 3A, and 3B). Furthermore, Applicants demonstrated that the reduction of NS1 expression in these cells augmented

expression of several interferon-response genes (Figure 5 - STAT1, STAT6, IRF1, IRF3, and IRF7 genes), which contribute to the human antiviral response.

At pages 3 and 4 of the Office Action, the Examiner indicates that Tuschl *et al.* provided "a general blueprint for the design, synthesis, and application of short interfering RNAs" and that "siRNAs are in general significantly more potent than ribozymes." However, although siRNAs may be "in general" significantly more potent than ribozymes, this does not mean that they will be effective in every setting or disorder. If this were the case, there would be no reason to carry out research with siRNA because one of ordinary skill in the art could simply rely on the fact that they will work.

Moreover, there is no empirical data, *in vitro* or *in vivo*, within the McSwiggen *et al.* patent to establish a proof of concept with ribozymes or any nucleic acid inhibitor to inhibit RSV in the relevant cells (*e.g.*, respiratory epithelial cells), and with which to create a reasonable expectation of success with siRNAs. Without having the benefit of this empirical data at the time the application was filed, one of ordinary skill in the art would not have a reasonable expectation of success in carrying out the method of the invention, which includes reduction of RSV gene expression and RSV viral titer in a human subject. Alternatively, if one of ordinary skill in the art was to take the teachings of the McSwiggen *et al.* patent at face value and presume the method using ribozymes to be effective, there would be no reason why one of ordinary skill in the art would have deviated from those teachings to use siRNA, as required by the currently pending claims. The Examiner cites the Chen *et al.* publication for teaching the use of siRNA expression vectors to prophylactically inhibit influenza infection in mouse lung. However, all respiratory infections are not the same and influenza infection is not the equivalent of RSV infection. RSV infection has its own pathogenesis.

It was the inventors of the subject application that determined that inhibition of RSV NS1 gene expression in interferon (IFN)-deficient Vero cells did not attenuate RSV infection, suggesting a role of the NS1 protein in the promotion of RSV infection by inhibiting the type-1 IFN pathway (see Example 1 at page 45 of the specification). The inventors verified that the NS1 decreases the amount of type-1 IFN by immunoblotting, microarray analyses, and translocation experiments (see Example 2 at pages 45-46 of the subject specification).

At the time the subject application was filed, the cited references would not have conferred a reasonable expectation of success in delivering a vector comprising a nucleic acid sequence encoding an siRNA to airway cells in a human *in vivo*, such that expression of a targeted RSV gene or transcript and RSV viral titer are reduced. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. MPEP §2143.01. Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976); MPEP §2143.02.

As described in Examples 4 and 5 at pages 47-48 of the specification, when administered two days before or two days after inoculation with RSV, a complex of chitosan and siRNA plasmid (NG042-siNS) targeting RSV NS1 was effective in reducing RSV NS1 expression and reducing RSV titers. Furthermore, lung sections of mice treated two days after RSV infection exhibited a significant decrease in lung inflammation.

Submitted herewith for the Examiner's consideration is the Zhang *et al.* publication (*Nature Medicine*, 2005, 11:56-62), a scientific publication co-authored by the inventors of the subject application. As described at page 52 of the subject specification and the Discussion section of Zhang *et al.*, the results of the inventors' studies on the prophylactic potential of NG042-siNS1 indicate that the NS-1-targeted siRNA induces substantial protection from RSV infection, infection-induced inflammation and airway reactivity, and the protective effect lasted for at least four days. Furthermore, even a single-dose prophylaxis considerably inhibits re-infection in mice that are administered a higher dose of RSV sixteen days after primary infection. Without being bound by theory of mechanism, the inventors propose that NS1 gene knockdown confers enhanced protection by augmenting the anti-RSV host immunity via enhanced IFN production, which prevents mice from RSV re-infection. Applicants respectfully submit that these results are unexpected in view of the references cited within the Office Action, particularly in view of the lack of empirical results contained within the cited references.

Accordingly, reconsideration and withdrawal of the rejection under 35 USC §103(a) is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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Attachment: Zhang *et al.*, *Nature Medicine*, 2005, 11:56-62